REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-50 are in the case.

I. ELECTION/RESTRICTION

The election of Group I is hereby affirmed. Claims 16-17, 42-46 and 50 are withdrawn from further consideration.

II. SAME INVENTION DOUBLE PATENTING

Claims 22, 24, 26 and 28-30 stand provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 48-53 and 62 of copending Application Serial No. 09/763,955. In response, and without conceding to the merit of this rejection, the claims of copending Application Serial No. 09/763,955 have been amended to delete reference to prevention of the recited condition. Same invention double patenting now no longer exists as between the two cases. Withdrawal of the double patenting rejection is respectfully requested.

III. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-15, 21, 23, 31-32, 37-41 and 47 stand provisionally rejected on obviousness-type double patenting grounds as allegedly unpatentable over claims 48-59 of copending Application Serial No. 09/763,955. Applicants will consider filing a Terminal Disclaimer when otherwise allowable subject matter is indicated.

IV. CLAIM OBJECTIONS

Claims 22 and 38 stand objected to in view of abbreviations appearing in the those claims. Claims 22 and 38 have been amended to meet the objection. Basis appears at page 23 and at page 29, penultimate line. No new matter is entered. Withdrawal of the objections is now respectfully requested.

V. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTIONS

Claims 1-15, 18-32 and 47-49 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the treatment of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction, allegedly does not reasonably provide enablement for the prevention of congenital mitochondrial disease, Alzheimer's Disease, Huntington's Disease, neuromuscular degenerative disease, and pathophysiological consequences of mitochondrial respiratory chain dysfunction. Claims 33-36 stand rejected under 35 USC 112, first paragraph, on alleged lack of enablement grounds based on the assertion that the examples fail to demonstrate that death or functional decline of post-mitotic cells is prevented by administration of a pyrimidine nucleotide precursor as claimed. The rejections are respectfully traversed.

The originally-filed specification is enabling for prevention as well as the treatment of the listed diseases. Hereditary mitochondrial diseases typically involve genetic defects in genes coding proteins that, directly or indirectly, affect mitochondrial respiration. Diseases of acquired mitochondrial dysfunction have molecular defects

disrupting mitochondrial respiration. The concept of "prevention" in the context of this class of diseases relates to clinical expression of symptoms stemming from the molecular defect. The idea of prevention does not relate to preventing or reversing genetic defects but, rather, compensating for them to prevent full clinical manifestation of their disorder.

Mitochondrial diseases generally worsen over time, especially during periods of metabolic stress like infections. One prevention threshold, for example, is preventing the need for frequent hospitalization of patients suffering from a mitochondrial disease during ordinary childhood infections, such as colds.

Prevention in the context of the present invention applies to reducing the rate of progression of a chronic, worsening disease process compared with patients who do not receive the drug. In many cases, this will also fall under the heading of "treatment" of a diagnosed disease but, in other situations, e.g. where a genetic disorder has not yet (but eventually will) cause clinical symptoms (e.g. in Huntington's Disease, where a hereditary defect leads to adult onset of the disease after a nonsymptomatic earlier life) or Alzheimer's Disease, when a patient can be detected occur before actually meeting the diagnostic criteria for Alzheimer's Disease, the concept of prevention is medically and scientifically legitimate. Thus, administration of compounds of the invention to genetically-diagnosed Huntington's patients prevents the onset of debilitating symptoms, lessen their severity once they do manifest, or slows their rate of progression.

In medical practice, these types of outcomes in progressive diseases are considered successful preventative interventions. In animal experiments, prophylactic

administration of a pyrimidine nucleotide precursor, triacetyluridine, reduced the effects of subsequent administration of mitochondrial toxins, e.g. 3-nitropropionic acid (Example 9) and MPTP (Example 7). Experiments with the Complex IV inhibitor sodium azide yielded similar results (Example 12). These same examples demonstrate prevention of death or damage to post-mitotic cells in the nervous system. It is not that the administered drug (triacetyluridine) prevented the chemical lesion caused by the toxin (and it likewise does not reverse the genetic lesion in a patient with hereditary or congenital mitochondrial disease) but, rather, it attenuated the physiological consequences of the chemical lesion, including prevention of mortality in some cases.

The correct connotation of "prevention" in the context of these diseases is prophylactic administration of compounds of the invention which prevents progression or full manifestation of diseases related to essentially irreversible mitochondrial defects. The specification is enabling with respect to such prevention in the context of the presently claimed invention. Just as few or no other classes of drugs used for treatment of chronic diseases prevent or reverse all symptoms completely, the standard for successful prevention in medical practice is prevention of symptoms of a disorder (especially a progressive or episodically exacerbating disorder) from being as bad as it would be without the drug. This is especially significant for mitochondrial disorders, which as a class often undergo exacerbations, either episodically or permanently.

The effect of an acylated ribonucleoside derivative(s) to "prevent" diseases involving mitochondrial dysfunction can be described as a "neuroprotective" and "cytoprotectective" effect (to include non-central nervous system cells). The term "neuroprotective" has been used to refer to the ability of a therapeutic method, if given

prior to the initial initiation of factors that cause the disease ("pretreatment"), to reduce the severity or delay the onset and/or slow the progression of tissue damage and functional impairment (see: Ferrante, et al., 2000; Du, et al., 2001; Ravina, et al., 2003, copies attached). The data included in the present application involve both "treatment" and "neuroprotective" effects of an pyrimidine nucleotide precursor(s), used as a therapeutic for disorders involving mitochondrial respiratory chain enzyme impairment. The present application has 15 figures that provide examples of both a treatment and a prevention component to the therapeutic effects of pyrimidine nucleotide precursor(s)against mitochondrial respiratory chain enzyme inhibitors. Mitochondrial Complex II enzyme activity was inhibited by 3-nitropropionic acid (3NP) as part of the experiments in Figures 1-12. Mitochondrial Complex IV enzyme activity was inhibited by azide as part of the experiments depicted in Figures 13-15.

The experimental paradigm involved initiating treatment with the pyrimidine nucleotide precursor triacetyluridine prior to the administration of the mitochondrial toxin. The complex I respiratory chain inhibitor MPTP model of Parkinson's disease (PD) (Example 7), Complex II respiratory chain inhibitor 3-nitropropionic acid model of Huntington's disease (HD) (Example 9) and the Complex IV respiratory chain inhibitor azide model of Alzheimer's disease (AD) included pretreatment with triacetyluridine. The treatment with triacetyluridine continued throughout the course of these examples. The sum therapeutic effect of triacetyluridine in the PD and HD and stroke models was a combined neuroprotective/cytoprotective and treatment effect. In the Complex IV respiratory chain inhibitor azide model of AD, there was a decrease in mortality due to pretreatment with triacetyluridine. If the mitochondrial impairment was not extremely

severe as was the case with the use of azide at only the 40 µg/hr dose, pretreatment/treatment with triacetyluridine was able to completely "prevent" mortality.

For all of the above reasons, it is believed that the specification as filed enables prevention as well as treatment in accordance with the claimed invention. Withdrawal of the outstanding 35 USC 112, first paragraph, rejections is accordingly respectfully requested.

VI. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 1-15, 18, 21-41 and 47-49 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons stated on page 9 of the Action. The Examiner asserts that the phrase "an effective amount" renders all claims in which it appears indefinite as the function which is to be achieved is not stated in the claims and more than one effect can be implied from the specification or relative art. The phrase "a pyrimidine nucleotide precursor" has also been objected to as allegedly rendering all claims in which the phrase appears indefinite. The Examiner asserts that, in the absence of distinct chemical core, distinct language to describe the structural modifications, or the chemical names of precursor compounds of this invention, the identity of the precursors would be difficult to describe. The Examiner further asserts that the metes and bounds of the precursor compounds applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims. The rejection is respectfully traversed.

The phrase "an effective amount" does not render the claims in which it appears indefinite. Based in the specification, particularly page 26, and the level of ordinary skill

in this art, the reader would have no difficulty in determining the effective amount of pyrimidine nucleotide required for the consequence of interest. The claims cover the treatment or prevention of any pathophysiological consequence of mitochondrial respiratory dysfunction. Conditions related to mitochondrial respiratory dysfunction are described in detail beginning in paragraph D on page 18 of the originally filed specification, and one of ordinary skill in this art would be able to determine the relevant effective amount based on the condition (consequence) under consideration. The fact that there are a significant number of conditions or consequences associated with mitochondrial respiratory dysfunction is not a reason to reject based on indefiniteness. Withdrawal of this aspect of the rejection is respectfully requested.

The phrase "a pyrimidine nucleotide precursor" is likewise not indefinite. The term is defined at page 10, and numerous examples are provided. Based on this disclosure, and the level of ordinary skill in this art, the reader would have no difficulty in understanding the phrase "a pyrimidine nucleotide precursor". Withdrawal of this aspect of the rejection is respectfully requested.

VII. THE OBVIOUSNESS REJECTION

Claims 1-15, 18-32 and 37-41 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Page et al in combination with U.S. 6,316,426 to von Borstel et al. That rejection is respectfully traversed.

Page describes the use of uridine to treat patients with a rare disease associated with excess activity of the enzyme 5'-nucleotidase, an enzyme involved in degradation of nucleotides. In scientific publications describing these patients (*see*: Page, et al.,

Adv. Exp. Med. Biol. 1998; 431:789-92 and Page et al., Adv. Exp. Med. Biol. 1991;309B:345-8, copies attached), there is no indication or suggestion of evidence for mitochondrial respiratory chain dysfunction as a molecular basis for 5'-nucleotidase excess. Applicants submit that the finding by Page that nucleotide precursors (uridine or ribose) are clinically useful in treating a disorder in which the only known molecular deficit is an excess of an enzyme (5'-nucleotidase) involved in nucleotide degradation, would **not** have led one of ordinary skill to suspect that uridine or ribose would be useful in treating or preventing conditions caused by mitochondrial respiratory chain dysfunction, even those which might manifest some similar symptoms. As noted above, patients with this condition are rare, and there are no clear implications for other diseases.

The above-noted deficiencies of Page are not cured by the '426 U.S. patent to von Borstel. The '426 U.S. patent discloses that acylated ribonucleoside derivatives are effective in treating a number of disorders that involve functional impairments in tissue and organ systems involving metabolic deficiencies. Therefore, even if Page and von Borstel would be combined to treat 5'-nucleotidase excess, one still would not have arrived at the claimed invention of treating or preventing pathophysiological consequences of mitochondrial respiratory chain dysfunction. Accordingly, no *prima facie* case of obviousness is established in this case. Withdrawal of the obviousness rejection is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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Attachments: Ferrante, et al., 2000; Du, et al., 2001; Page et al. (1991), Page et al. (1998), Ravina, et al., 2003; IDS; PTO 1449, IDS fee